Initial factors predicting rebleeding and death in bleeding peptic ulcer disease

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ABSTRACT

Objective: Bleeding peptic ulcer constitutes approximately half of the cases admitted with upper gastrointestinal bleeding. Although the bleeding episode stops spontaneously in most of them, rebleeding occurs in as much as 10-30% of them and has a mortality rate of 5-10%. In this study, we have evaluated the possible significant predictors associated with this adverse outcome.

Methods: The records of 205 patients admitted to gastrointestinal bleeding unit (GIBU) in Riyadh Central Hospital, during the period May 1996 through to April 1999, with endoscopic confirmed diagnosis of bleeding peptic ulcer disease were reviewed for demography, clinical presentation, hematology, biochemistry, initial blood pressure, nasogastric lavage color, co-morbid disease and endoscopic findings. All the significant factors found initially ($P<0.05$) were entered into odds ratio and its 95% confidence interval and finally the unconditioned logistic regression model was used to find out the significant independent predictors for both rebleeding and mortality in these patients.

Results: The majority of patients (85%) were males and below the age of 60 (73%). Duodenal ulcer was the source of bleeding in 84%. Endoscopy was performed in all patients within 24 hours of admission. Only 15% were actively bleeding at the time of initial endoscopy. Thirty-six patients (17%) rebelled, majority within 72 hours of initial hemostasis. Overall, 11 patients (5%) died, 6 of them were rebleeders. Initial presentation of systolic blood pressure <100 mm Hg, blood in nasogastric tube and visible vessel within the ulcer in endoscopy were independent predictors of rebleeding while initial systolic blood pressure <100 mm Hg and age >60-years were independent predictors of mortality.

Conclusion: Improvement of outcome in patients with bleeding peptic ulcer disease can be achieved by early detection of those patients who are at risk of adverse outcome. Patients with the above mentioned independent predictors of rebleeding and mortality are best managed in the intensive care unit with endoscopic hemostasis and proton pump inhibitor (PPI) therapy for a minimum of 5-days of admission.

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Acute upper gastrointestinal bleeding is quite a common reason for emergency admission and in approximately 50% of these cases, the diagnosis is bleeding peptic ulcer disease (BPUD).[1,2] The bleeding episode usually stops spontaneously in as much as 50-80% of such cases.[2] Since 1970 endoscopic therapy remains the initial treatment of choice for such patients. With the advances in endoscopic hemostatic techniques, like adrenaline and sclerosant injections, electrocoagulation, heat probe coagulation, hemoclip application and fibrin glue sealing, the rate of initial hemostatic success rises to 97% but the incidence of rebleeding remains relatively high (10-30%) in patients with BPUD.[3-6] The reported mortality from BPUD is 5-10%.[7,8] Since the mortality in patients with BPUD is mainly

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related to rebleeding, identification of those patients who are at a higher risk of rebleeding, and hence death, will help to treat them early and minimize adverse outcome. In the past few years, this matter was extensively studied and different endoscopic and clinical risk factors have been evaluated.[9-13] More recently, most of the papers are evaluating the endoscopic stigmata for the risk of rebleeding in BPUD.[14-17] Some scoring systems and mathematical models have been proposed for that purpose to stratify the patients with BPUD into different outcome groups.[18-20] This retrospective study on 205 patients with BPUD admitted to a specialized gastrointestinal bleeding unit (GIBU) in Riyadh Central Hospital, presents the effect of the various clinical and endoscopic factors on rebleeding and mortality.

Methods. In this retrospective analysis, the records of 205 patients admitted to GIBU with the diagnosis of BPUD during May 1996 through to April 1999 were reviewed for possible risk factors for adverse outcome. The data collected includes patients' demography, clinical presentation, initial blood pressure (BP), color of nasogastric lavage (NGL), hematology, biochemistry, co-morbid disease, endoscopic stigmata of bleeding, hospital course and outcome (rebleeding and death). The variables tested, and there categorizations are presented in **Table 1**. The diagnosis of BPUD was confirmed by endoscopy in all patients. It was carried out immediately in unstable patients and within 24-hours in stable patients. The description of the endoscopic stigmata were collected from the endoscopy records. Other factors which were evaluated also includes non-steroidal anti inflammatory drugs (NSAID), warfarin, ulcer medications, past history of peptic ulcer disease or surgery and blood transfusion requirement. In patients with rebleeding, the form of further management (reendoscopy or surgery, or both) were recorded. The cause of death was also recorded in mortality group. Adverse outcome is defined as rebleeding, surgical intervention and death during the same hospitalization. Rebleeding was defined if one or more of the following were found after initial spontaneous or endoscopic hemostasis: 1. Recurrence of hematemesis or positive NGL. 2. Recurrence of melena after normalization of stool color. 3. Serial drop of hemoglobin despite blood transfusion. 4. Unstable vital signs after a period of stabilization.

Statistical analysis. Statistical package for social sciences version 9 was used for data tabulation and analysis. The student test was used to compare between means, while the Z-test was used for proportions drawn from 2 samples. Odds ratio (OR) and its 95% confidence interval (CI)

Table 1 - Categorized variables tested for risk factors of rebleeding and mortality.

Variable	Categories
Age (years)	<60, >60
Sex	Male, Female
Nationality	Saudi, Non Saudi
Presentation	Hematemesis, Malena, Both
Gastric lavage	Bloody, Clear
Admission systolic BP (mm Hg)	≥100, <100
Admission diastolic BP (mm Hg)	≥60, <60
Blood transfusion (Units)	≤6, >6
Comorbid disease	≤1, 1-2, >2
Ulcer site	Gastric, duodenal, stomal
Endoscopic stigmata	Active bleeding, recent bleeding, visible vessel, clean base ulcer
Urea (n=1.8-7.1 mmol/L)	≥8, <8
Serum creatinine (n=62-106 mmol/L)	≥110, <110
Jaundice	Present, Absent
Ascites	Present, Absent

BP - blood pressure

Table 2 - Endoscopic stigmata and risk of rebleeding and mortality.

Endoscopic findings	Entire group (n=205)	Rebleeding group (n=36)	Mortality group (n=11)
Duodenal ulcer (n=172) (83.9)			
Active bleeding			
Visible vessel	14	10	3
No vessel	11	2	1
Recent bleeding			
Visible vessel	20	9	1
No vessel	98	12	4
Kissing	15	-	2
Not bleeding	14	-	-
Gastric ulcer (n=28 (13.7)			
Active bleeding			
Visible vessel	1	-	-
No vessel	4	2	-
Recent bleeding			
Visible vessel	2	-	-
No vessel	21	-	-
Stomal ulcer (n=5) (2.4)			
Active bleeding	2	-	-
Recent bleeding	3	-	-

Table 3 - Association between variables studied and risk of rebleeding and mortality (*P* values).

Variables	Entire group (n=205)	Rebleeding group (n=36)	*P* value	Mortality group (n=11)	*P* value
Age (in years)					
<60	150 (93.2)	29 (19.3)	NS	4 (2.7)	NS
>60	55 (26.8)	7 (12.7)	0.24	7 (12.7)	0.0019
Sex and nationality					
Sex					
Male	175 (85.4)	33 (91.7)	NS	10 (90.9)	NS
Female	30 (14.6)	3 (8.3)		1 (9.1)	
Nationality					
Saudi	83 (40.5)	10 (27.8)	NS	6 (54.5)	NS
Non-Saudi	122 (59.5)	26 (72.2)		5 (45.5)	
Presentation					
Hematemesis	26 (12.7)	4 (11.1)	NS	2 (18.2)	NS
Melena	82 (40)	6 (16.7)	NS	2 (18.2)	NS
Hematemesis and melena	97 (47.3)	26 (72.2)	0.0025	7 (63.6)	0.314
Gastric lavage positive for blood	94 (45.9)	31 (86.1)	0.00001	10 (90.9)	0.0056
Admission BP (mm Hg)					
Systolic BP					
≥100	186 (90.7)	22 (11.8)	0.00001	5 (2.7)	0.007
<100	19 (9.3)	14 (73.7)	0.00001	6 (31.6)	0.00001
Admission hemoglobin	9.127	7.319	0.0001	7.1	0.0142
Diastolic BP (mm Hg)					
Mean	76.24	64.167	0.00001	51.818	0.00001
Blood transfusion, units of blood					
≥5	26	13	0.0001	5	0.033
Comorbid disease					
≤1	47	11	NS	1	NS
1-2	24	3	NS	2	NS
>2	16	7	0.0005	8	0.00001

BP - blood pressure, *P*<0.05 significant, NS - not significant

were used to assess the risk of re-bleeding and death in relation to the studied variables. All factors proved to have significant association with re-bleeding or death in crude analysis were entered into unconditional logistic regression model to determine the independent predictors of re-bleeding or death.

Results. Over a period of 36-months, 205 patients were admitted to GIBU, Riyadh Central Hospital with the diagnosis of BPUD. The mean age was 47.5 years (range 12-98 years), most of them were below the age of 60-years (73.2%). Non-Saudi nationals comprised 59.5%, and there was male preponderance (85.4%). Upper gastrointestinal (GI) endoscopy revealed duodenal ulcer in 172 patients (84%), gastric ulcer in 28 patients (14%) and anastomotic stomach ulcer in 5 patients (2%). Active bleeding at initial endoscopy was found in 30 patients (15%), 15 of them were bleeding from a visible vessel in the bed of the ulcer. Most patients (n=175, 85%) were not actively bleeding at the initial endoscopy. Nonbleeding visible vessel (NBVV) was noted in 22 patients **(Table 2)**. Associated nonbleeding esophageal varices were seen in 12 patients. The total number of patients who experienced adverse outcome was 46 (22%). Thirty-six patients rebled, for which surgery was required to arrest bleeding in 29 patients. One patient developed duodenal perforation following endoscopic adrenaline injection of the ulcer for which he was operated. In the remaining 6 patients rebleeding was controlled by endoscopic means. Overall, 11 patients (5%) died, 6 of them were rebleeders. Two patients died following surgery to arrest the bleeding. Others (n=9) died due to aggravation of their co-morbid disease following initial bleeding or rebleeding episode. The univariate analysis of all the tested variables are presented in **Table 3**. When the significant variables (*P*<0.05) were further tested using the OR and CI, only 8 factors were found to be significant risk factors for rebleeding or mortality, or both **(Table 4)**. Most BPUD patients

Table 4 - Risk factors for rebleeding and death (odds ratio and its 95% CI).

Factors	Rebleeding		Death	
	Odds ratio	95% CI	Odds ratio	95% CI
Age >60	0.6	0.22-1.60	8.23*	2.28-29.71*
Male	2.09	0.56-9.22	1.76	0.22-14.26
Non-Saudi	1.98	0.9-4.36	0.55	0.16-1.86
Hematemesis	2.3	0.49-10.43	3.33	0.31-35.56
Hematemesis and Melena	2.1	0.58-7.65	3.11	0.57-22.36
SBP <100 mm Hg	14.91*	4.66-47.66*	13.16*	3.09-56.06*
DBP <60 mm Hg	27.1*	3.06-239.93*	23.88*	4.15-137.34*
Hb <8 gm/dL	2.42*	1.16-5.03*	7.3*	1.53-34.7*
Endoscopic findings				
Active bleeding	5.34*	2.33-12.44*	3.39	0.93-12.23
Visible vessel	10.27*	4.43-23.81*	2.05	0.51-8.17
Transfusion >5 units	39*	7.02-285.62*	18.81*	1.94-499.67*
Co-morbid disease	1.27	0.58-2.76	6.69*	1.3-46.17*
Gastric lavage +ve for blood	10.43*	3.86-28.21*	13.1*	1.64-104.31*

* statistically significant, SBP - systolic blood pressure, CI - confidence interval
DBP - diastolic blood pressure, Hb - hemoglobin, +ve - positive

Table 5 - Significant independent predictors of rebleeding and mortality (multivariate logistic regression model).

Predictive factor	Rebleeding		Mortality	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Age >60 years	NS	NS	5.79	1.03-31.70
Endoscopic finding of visible vessel	8.58	2.9-25.38	NS	NS
Gastric lavage +ve for blood	5.06	1.63-15.67	NS	NS
Systolic blood pressure <100 mm Hg	8.15	1.69-39.26	7.44	1.01-54.55

NS - not significant, OR - odds ratio
CI - confidence interval, +ve - positive

were <60-years. No statistical difference in rebleeding was observed in, <60 or >60-years age group, but mortality was higher among >60-years age group (OR: 8.23, CI: 2.28-29.71). The mean admission BP was significantly associated with outcome. Out of 19 patients with admission systolic BP of <100 mm Hg, 14 patients rebled (OR: 14.91, CI: 4.66-47.66) and 6 patients died (OR: 13.16, CI: 3.09-56.06). Similarly, initial diastolic BP <60 mm Hg was associated with a higher risk for rebleeding (OR: 27.1, CI: 3.06-239.9) and mortality (OR: 23.88, CI: 4.15-137.34). Admission hemoglobin of <8 g/dL was shown to be a significant predictor of rebleeding (OR: 2.42, CI: 1.16-5.03) and mortality (OR: 7.3, CI: 1.53-34.7). Amount of blood given to a patient were significantly associated with outcome. Those who required >5 units had higher risk for rebleeding (OR: 39.0, CI: 2.26-67.16) but was not shown to be significant for mortality. Presence of blood in nasogastric tube upon admission was a highly significant predictor of rebleeding or death. Among rebleeders, 86% presented with blood in nasogastric tube on admission (*P*=0.00001) (OR: 10.43, CI: 3.86-28.2) where as 91% from the mortality group had blood in their nasogastric tube (*P*=0.0077) (OR: 13.1, CI: 1.64-104.31). Presence of visible vessel in the ulcer bed whether actively bleeding or not was significantly associated with rebleeding (OR: 10.27, CI: 4.43-23.81). There were 37 patients with visible vessel, only 15 of them were actively bleeding which was controlled by endoscopic therapy. Twenty patients from this group subsequently rebled resulting in 4 deaths. Co-morbid diseases were present in 87 patients (42%). It had significant effect on the mortality (OR: 6.69, CI: 1.3-46.17). Co-morbid diseases were present in 9 patients out of 11 patients who died. Bleeding episode usually aggravated the co-morbid disease status leading to death. Among the 36 patients who had rebleeding, 26 patients (72%) rebled within 72 hours, and in all within 5 days of initial hemostasis. The overall mean hospital stay was 8.22 days ± 5.317, but it was significantly prolonged in patients with rebleeding (mean=12.083 days, *P*=0.00001). The factors with significant association of rebleeding or death in crude analysis were entered into unconditional logistic regression model to determine the independent predictors of rebleeding or death (**Table 5**). The endoscopic finding of visible vessel (adjusted OR: 8.58, Cl: 2.9-25.38), admission systolic blood pressure <100 mm Hg (adjusted OR: 8.15, Cl: 1.69-39.26) and the presence of blood in NGT (adjusted OR: 7.44, Cl: 1.01-54.55) were

found to be independent predictors of rebleeding, while systolic BP <100 mm Hg and age >60-years (adjusted OR: 5.79, Cl: 1.07-31.70) were independent predictors of death.

Discussion. Bleeding in patients presenting with BPUD stops spontaneously in most cases. Endoscopic treatment has improved the initial hemostasis to over 90%, but, rebleeding rate remains high (10-30%).[3-6] The mortality from BPUD remains 5-10%.[7,8] Rebleeding is considered an important risk factor for mortality in these cases,[21] hence, the need to identify those factors that can help identify patients at higher risk for rebleeding. In our study, rebleeding occurred in 36 patients (17.4%), and was the cause of death in 6 of 11 patients who died. Several clinical and endoscopic predictors for rebleeding and mortality in patients with BPUD have been reported in the literature.[9-13,22-24] These include: shock, endoscopic stigmata, hematemesis, blood in nasogastric tube, age and comorbid disease. In the present study, the variables that showed to be significant risk factors for rebleeding and mortality were assessed using the OR and its 95% CI. Such crude analysis has revealed 8 significant risk factors for adverse outcome in BPUD patients. These factors were systolic blood pressure <100 mm Hg, diastolic blood pressure <60 mm Hg, hemoglobin level <8 g/dL, positive blood in nasogastric tube, transfusion >5 units of blood, endoscopic finding of visible vessel, age >60-years and comorbid disease. However, when these risk factors were entered into unconditional logistic regression model to find out the significance of each variable related to the others only 4 independent predictors of either rebleeding or mortality were observed. Shock and major stigmata of recent bleeding have been reported by many authors as the main predictors of rebleeding.[25-27] In the present study, we have found that the admission systolic BP <100 (shock) is a significant independent predictor of both rebleeding and mortality. Stigmata of recent bleeding (adherent clot on the ulcer and nonbleeding visible vessel –NBVV) are reported predictors of rebleeding and mortality.[16] In the present study, even though the endoscopic finding of active bleeding, and nonbleeding visible vessel were significant risk variables, in the final logistic regression the visible vessel was the only endoscopic stigmata considered an independent predictor for rebleeding (adjusted OR: 8.58, CI: 2.9-25.38). It was however, not significant independent predictor for mortality. Hematemesis (vomiting blood) has been reported by some authors as significant predictor of rebleeding,[13,28,29] but in our study, it was found not a significant predictor for adverse outcome. Similar observation has been reported by Perng et al.[9] The presence of blood in nasogastric tube upon initial presentation was not considered an important predictor of rebleeding by most authors except Perng et al.[9] In the present study, there was an association between blood in NGT on presentation and rebleeding. Among the 36 patients who rebled, 31 patients presented with blood in nasogastric tube. The logistic regression model revealed this finding as a significant independent predictor for rebleeding (OR: 7.44, CI: 1.04-54.55) but not so for mortality. The number of blood transfusion (>5 units), co-morbid disease and the age were not found to be significant independent predictors for rebleeding in this study. However, age and co-morbid disease were found to be significant factors affecting mortality in the study. Other studies have supported this observation.[30-33] The other important finding in the present study is that around 72% of rebleeding occurred within 72 hours, and in all within 5 days. We feel that this observation will help physicians in deciding discharge time for these patients. The prevention of further hemorrhage in high risk patients has received much attention in recent reports. Prophylactic or elective endoscopy has been explored with some promising results in lowering the rebleeding rate.[14-17] Lin et al[17] however, have shown that omeprazole (proton pump inhibitor) was the most important factor preventing the rebleeding after endoscopic hemostasis with multipolar electrocoagulation (MPEC).

We conclude that in patients with BPUD, the initial presentation with systolic BP <100 mm Hg, blood in nasogastric tube and endoscopic presence of visible vessel are independent predictors of rebleeding, while a systolic BP <100 and age >60-years are independent predictors for mortality. These patients should have early endoscopic therapy, omeprazole and continuously monitored in intensive care unit. As most of the rebleeding occurs within 5 days these patients should be kept under observation for at least one week.

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